11-15-85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of additional data on a chronic feeding study in rats (Bayer Report No. 4888, Mobay Report No. 41816) submitted by Mobay in support of the Registration Standard on Metribuzin (Sencor) EPA ID #3125-270; EPA Accession #258756 & 258757; EPA Record #156177; Shaugnessy #101101-4; Caswell #339, Tox Branch Project No. 208.

TO: Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 11/14/85
Pharmacologist, Review Section V
Toxicology Branch/HED (TS-769C)

THRU: Laurence D. Chitlik, D.A.B.T. W. Testers for L. Chitlik 11/14/85
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and
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and
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Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Mobay Chemical Corporation
Agricultural Chemicals Division
Kansas City, Missouri 64120

Action Requested: Review additional data for the rat oncogenicity study with Metribuzin (Sencor), submitted in support of the Registration Standard for the chemical.

Recommendations:

The sponsor has now satisfactorily responded to all requests made in the review conducted for the Registration Standard of the chronic rat study and the study can now be upgraded to Core-Minimum Data. Assessment of the chronic toxicity/oncogencity potential for metribuzin in the rat has included the additional data and clarifying information provided by the registrant.

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Metribuzin is not oncogenic to the rat in dietary levels up to 300 ppm. The No Observed Effect Level (NOEL) for systemic effects is 100 ppm. The Lowest Observed Effect Level (LOEL) for systemic effects is 300 ppm, based on the decreased weight gain, along with the pathological changes in the liver, kidneys, uterus and mammary glands.

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The additional data reviewed here were for the study identified as follows:

Study Title: BAY 94 337 Chronic Toxicity Studies on Rats (2-year feeding experiment).

EPA Identification Numbers: EPA Accession No. 112891

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: BAYER AG
Institut fur Toxikologie
Wuppertal-Elberfeld

Report Numbers: Bayer AG Report No.4888 & Mobay Ag Chem No.41816

Date of Study: September 25, 1974

Study Director: Dr. rer. nat. Eckhard Loser

Histopathological Examination: Prof. Dr. med. U. Mohr

Test Compound: BAY 94 337 (Metribuzin) Technical (also called SENCOR)
Purity: 99.5%
Batch No.: 1603/71

Dosage: 25, 35, 100 and 300 ppm mixed with pulverized Altromin R feed (from Altrogge, Lage/Lippe).

Test Animal: SPF Rats (Wistar Strain) bred by Winkelmann, Kirchborchen, Kreis Paderborn. At start of experiment rats were about 28 to 32 days old with males having a mean body weight of 51.4 cm. and females with a 52.1 gm mean body weight.

Materials and Methods: A copy of the materials and methods section from the investigators report is appended.

The relevant item in this section of the review of the study which pertains to the additional data reviewed here is as follows:

The investigators examined all tissues that are required by CORE, however histopathology was performed on all animals only in control and the high dose group. In the other three dose groups only selected tissues in selected animals (10 per group) were examined.

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Background:

During preparation of the Registration Standard for Metribuzin, the two year chronic feeding study in rats (Bayer AG Report No.4888, Mobay Report. No.41816, dated 9/25/74) was re-reviewed and classified as Core-Supplementary Data since the oncogenic potential of metribuzin in this species could not be fully assessed without consideration of additional data and clarification of certain pathological terminology. The re-review found a statistically significant increase in liver bile duct adenomas ($p < 0.01$) and pituitary adenomas ($p < 0.05$), as well as an increase in ovarian adenoma in females of the 300 ppm test group. There were statistically significant increases in the non-neoplastic finding of liver "changes in the nucleus" in the females of the 300 ppm test group ($p < 0.01$, males also showed a slight increase). However, all the animals of the 25, 35 and 100 ppm test groups had not been examined and a complete evaluation of the oncogenic potential could not be accomplished without these additional data.

It was concluded that there was no evidence of a compound related effect on hematological, clinical-chemical, urinalysis, kidney function, liver function and thyroid function test parameters.

The following are the data and/or clarifications requested:

a. Histopathological examination of the liver and pituitary gland of the animals not previously examined in the 23, 35 and 100 ppm test groups. The registrant was directed to provide individual as well as summarized data.

b. Historical control data on the incidence of histopathological findings in the rat strain used.

c. Explanation of the finding called "tumor".

d. Explanation of the finding called "changes in the nucleus".

e. A table of weekly body weight data divided by sex for each study group.

The registrant responded with the following data and/or clarifying information:

a. An addendum (Addendum 2) to Report No. 41816 which contained tables presenting histopathological findings from additional animals in the 25, 35 and 100 ppm groups along with histopathological data from all the animals tested. This included a re-evaluation of liver findings and of the observation called "tumor".

b. Legible copies of life tables were provided.

c. Legible copies of the body weight tables which had been requested in a telephone conversation with the registrant.

d. Histopathological historical control data (Mobay Report No. 90236) from chronic studies using the same strain as used in the metribuzin study and run at approximately the same time period.

e. During telephone conversations between the registrant's pathologist and Dr. Louis Kasza, pathologist for the Toxicology Branch, the following items were clarified:

1. Reclassification of liver bile duct proliferative changes.
2. Clarification of the term "changes in the cell nucleus" of the liver.
3. Definition of the term "tumor",as used in the original report.

Results:

1. Adequacy of dosage levels.

The dosage range selected for this study is consistent with the observations noted in 2 ninety day sub-chronic feeding studies that were conducted in rats. Data from the chronic study indicated that the high dose (300 ppm) produced minimally toxic effects in the form of slightly lower body weights of both sexes, increased mortality in the males and increased incidences of minor histopathological changes in the females This is consistent with the concept of the maximum tolerated dose (MTD) as discussed in the Standard Evaluation Procedure, Toxicity Potential: Guidance for Analysis and Evaluation of Subchronic and Chronic Exposure Studies, June 1985.

2. Histopathological Findings

The registrant provided additional histopathological data on the animals of the 25, 35 and 100 ppm test groups, as well as a re-evaluation of the neoplastic findings. Tables I and II below present a summary of the combined observed findings (tables prepared by the reviewer). The registrant also provided historical control data from rat chronic studies using the same strain and conducted at approximately the same time period as the metribuzin study (although not conducted in the same test facility). These data are shown in Table I under the heading "Historical".

A. Neoplastic Findings

The following Table I presents the summary of the neoplastic findings.

Table I: Neoplastic Findings for BAY 94 337 (Metribuzin)

A: Male Rats

ORGAN	DOSE(ppm):	Control	25	35	100	300	Historical
Pituitary	#†	62	29	32	29	29	609
Adenoma		8(13%)	6(21%)	2(6%)	5(17%)	5(17%)	123(20%)
Adenocarcinoma		2(3%)	0	0	0	1(4%)	3(0.5%)
Thyroid	#	72	21	35	34	37	650
Adenoma		0	2(10%)	1(3%)	0	2(5%)	55(9%)
Adenocarcinoma		0	0	0	0	0	8(1%)
Adrenals	#	66	31	34	37	37	724
Medullary adenoma		6(9%)	2(7%)	1(3%)	0	1(3%)	-
Cortical adenoma		0	1(3%)	0	0	0	3(0.4%)
Pheochromocytoma		0	0	1(3%)	0	1(3%)	50(7%) ††
Testes	#	66	31	32	30	29	760
Leydig's cell tumor		3(5%)	2(7%)	1(3%)	0	0	24(3%)
Epididymides	#	66	21	22	20	29	450
Papillary cystoma		0	0	1(5%)	0	0	1(0.2%)
Prostate	#	65	31	32	30	29	381
Adenoma		0	1(3%)	0	0	0	0
Stomach	#	66	31	32	30	29	413
Carcinoma(forestomach)		1(2%)	0	0	0	0	0
Intestines	#	66	31	32	30	29	405
Adenocarcinoma		1(2%)	0	0	0	0	0
Kidneys	#	73	39	38	38	37	765
Papillary adenocarcinoma		1(1%)	0	0	0	0	2(0.3%)
Pancreas	#	65	22	23	30	29	435
Islet cell adenoma		0	0	0	1(3%)	0	9(2%)
Exocrine adenoma		0	1(5%)	0	0	0	-
Malignant schwannoma		0	0	0	1(3%)	0	-

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Table I continued:

ORGAN	DOSE(ppm):	Control	25	35	100	300	Historical
B. Female Rats							
Pituitary	#	71	34	31	33	35	676
Adenoma		16(23%)	6(18%)	9(29%)	11(33%)	14(40%)	148(22%)
Adenocarcinoma		11(16%)	1(3%)	0	0	7(20%)	5(0.7%)
Myxomatous cranio-pharyngioma		1(1%)	0	0	0	0	-
Thyroid	#	73	37	31	36	36	665
Adenoma		3(4%)	0	2(7%)	3(8%)	1(3%)	68(10%)
Adenocarcinoma		0	1(3%)	0	0	0	6(0.9%)
Adrenals	#	75	37	31	37	35	754
Medullary adenoma		0	1(3%)	0	0	0	-
Cavernous hemangioma		0	0	0	0	1(3%)	-
Uterus	#	72	34	31	32	35	718
Myoma		1(1%)	0	0	0	0	2(0.3%)
Adenomcarcinoma		1(1%)	1(3%)	1(3%)	1(3%)	1(3%)	44(6%)
Leiomyosarcoma		0	0	1(3%)	0	0	0
Ovaries	#	73	37	32	36	39	710
Granulosa cell tumor		0	1(3%)	1(3%)	0	0	5(0.7%)
Myxoma		0	1(3%)	0	0	0	-
Mammary Glands	#	72	30	25	19	35	-
Adenofibroma		4(6%)	5(17%)	2(8%)	2(11%)	1(3%)	-
Fibroadenoma		1(1%)	1(3%)	1(4%)	2(11%)	1(3%)	23 †††

† = Total examined - tissue samples
†† = includes malignant pheochromocytoma findings
††† = findings in 11 studies

Data extracted from Bayer Report No. 4888 Histopathology Addendum and Addendum 2.

Table I presents the "updated" (including the additional animals) neoplastic findings from the 2 year chronic rat study. As can be seen from this summary table (prepared by this reviewer) there were no biologically significant differences for neoplastic findings between any of the treated groups and both concurrent and historical controls for the males. Females fed levels of 35 ppm and above showed a dose-related increase in pituitary adenomas (23, 18, 29, 33 and 40% respectfully for control, 25, 35, 100 and 300 ppm study groups, statistically significant at the high dose, no differences noted in the grading of the lesions). The incidence for this tumor in males of the treated groups did not differ significantly from that of the control group. The historical control incidence for this particular observation averages 22% for 9 studies; however, the incidence in each of four of the individual historical control studies approached 40% (for females in 2 of the studies and for males in 2 different studies). There were no neoplastic findings in the liver of either sex (since "bile duct adenoma" was redefined as bile duct proliferation, see Table II); also, the incidence of ovarian adenomas was reassessed by the registrant and reduced (see section 3, below).

B. Non-neoplastic Findings

The following Table II presents the summary of the non-neoplastic findings.

Table II: Non-neoplastic Findings for BAY 94 337 (Metribuzin)

A: Male Rats

ORGAN	DOSE(ppm):	Control	25	35	100	300
Trachea	#	66	29	32	30	29
Hemorrhage		1(2%)	0	0	1(3%)	1(4%)
ICI ††		2(3%)	2(7%)	2(6%)	1(3%)	2(7%)
Heart	#	75	39	38	38	38
Hemorrhage		0	1(3%)	0	0	0
ICI		16(21%)	7(18%)	5(13%)	8(21%)	11(29%)
Scar		13(17%)	17(44%)	17(45%)	16(42%)	12(32%)
Edema		0	2(5%)	0	1(3%)	0
Lungs	#	74	39	38	37	38
Atelectasis		6(8%)	4(10%)	1(3%)	6(16%)	0
Hemorrhage		7(10%)	1(3%)	0	1(3%)	0
Hyperplasia – bronchial mucosa		0	0	1(3%)	0	1(3%)
Bronchitis		27(37%)	4(10%)	8(21%)	5(14%)	12(32%)
Emphysema		39(53%)	20(51%)	20(53%)	16(43%)	18(47%)
Parasitic cell granuloma		0	0	0	0	1(3%)
Edema		1(1%)	2(5%)	1(3%)	1(3%)	2(5%)
Peribronchial lymphocytic infiltration		35(47%)	33(85%)	29(76%)	22(60%)	15(40%)
ICI		0	4(10%)	0	0	0
Pneumonia		12(16%)	3(8%)	4(11%)	5(14%)	5(13%)
Foam cells in the alveoli		12(16%)	4(10%)	4(11%)	5(14%)	2(5%)
Liver	#	74	39	38	38	38
Dissociation		3(4%)	5(13%)	7(18%)	8(21%)	5(13%)
Fatty change (& fat)		65(88%)	12(31%)	11(29%)	10(26%)	29(76%)
Parasitic cell granuloma		4(5%)	2(5%)	2(5%)	9(24%)	6(16%)
Bile duct proliferation †††		19(26%)	9(23%)	7(18%)	10(26%)	9(23%)
Nuclear changes		5(7%)	10(26%)	6(16%)	3(8%)	4(11%)
Necrosis		4(5%)	2(5%)	0	2(5%)	2(5%)
Edema		4(5%)	3(8%)	1(3%)	2(5%)	1(3%)
Spleen	#	74	39	38	38	37
Giant cells		1(1%)	0	0	0	1(3%)
Kidneys	#	73	39	38	38	37
Cysts		0	0	1(3%)	1(3%)	3(8%)
ICI		7(10%)	0	0	2(5%)	0
Glomerular damage		0	0	1(3%)	0	0
Scar		1(1%)	3(8%)	3(8%)	2(5%)	0
Tubule proliferation		5(7%)	2(5%)	3(8%)	0	0
Renal pelvis proliferation		1(1%)	0	0	0	1(3%)
Cast		39(53%)	15(39%)	11(29%)	9(24%)	13(35%)

continued

Table II continued:

ORGAN	DOSE(ppm):	Control	25	35	100	300
Adrenals	#	66	31	34	37	37
Fatty change		0	0	2(6%)	4(11%)	1(3%)
Stomach	#	66	31	32	30	29
Hemorrhage		0	1(3%)	1(3%)	0	0
Cyst		0	1(3%)	0	0	0
ICI		0	3(10%)	1(3%)	2(7%)	0
Calcium concretions		1(2%)	3(10%)	0	0	0
Urinary bladder	#	65	21	25	20	28
Calcium concretions		0	0	3(12%)	1(5%)	0
Skeletal Muscle	#	66	29	32	29	29
Parasitic cell granuloma		1(2%)	0	0	0	0
Testes	#	66	31	32	30	29
Atrophy		5(8%)	7(23%)	0	2(7%)	0
Sperm detected		64(97%)	9(29%)	10(31%)	10(33%)	29(100%)
Epididymes	#	66	21	22	20	29
Atrophy		0	3(14%)	0	2(10%)	0
Thyroid	#	72	21	35	34	37
Cysts		0	1(5%)	0	1(3%)	0
B. Female Rats						
Trachea	#	71	33	28	32	35
Hemorrhage		0	1(3%)	3(11%)	0	0
ICI		2(3%)	3(9%)	1(4%)	1(3%)	1(3%)
Heart	#	77	37	36	40	39
Hemorrhage		2(3%)	2(5%)	0	0	1(3%)
ICI		23(30%)	1(3%)	1(3%)	5(13%)	5(13%)
Scar		16(21%)	13(35%)	16(44%)	20(50%)	8(21%)
Edema		0	0	0	0	2(5%)
Lungs	#	76	38	36	39	39
Atelectasis		9(12%)	2(5%)	2(6%)	7(18%)	4(10%)
Hemorrhage		4(5%)	1(3%)	0	0	0
Hyperplasia - bronchial mucosa		0	0	0	0	2(5%)
Bronchitis		12(16%)	4(11%)	6(17%)	3(8%)	2(5%)
Emphysema		56(74%)	15(40%)	16(44%)	15(39%)	11(28%)
Parasitic cell granuloma		1(1%)	0	0	0	0
Edema		1(1%)	1(3%)	0	0	1(3%)
Peribronchial lymphocytic infiltration		53(70%)	19(50%)	28(78%)	21(54%)	16(41%)
ICI		0	0	0	0	0
Pneumonia		3(4%)	4(11%)	2(6%)	2(5%)	2(5%)
Foam cells in the alveoli		3(4%)	4(11%)	5(14%)	1(3%)	2(5%)

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Table II continued:

ORGAN	DOSE(ppm):	Control	25	35	100	300
Liver	#	76	38	36	39	39
Dissociation		0	3(8%)	3(8%)	2(5%)	0
Fatty change (& fat)		71(93%)	10(26%)	10(28%)	10(26%)	35(90%)
Parasitic cell granuloma		0	0	1(3%)	0	0
Bile duct proliferation	†††	13(17%)	6(16%)	9(25%)	5(13%)	19(49%)
Hypertrophy/hyperplasia		0	3(8%)	3(8%)	0	0
Nuclear changes		10(13%)	1(3%)	3(8%)	7(18%)	6(15%)
Necrosis		0	2(5%)	0	0	0
Edema		0	0	2(6%)	0	0
Spleen	#	77	38	36	39	39
Giant cells		0	0	0	0	2(5%)
Kidneys	#	77	38	36	39	39
Cysts		1(1%)	1(3%)	1(3%)	1(3%)	1(3%)
ICI		2(3%)	2(5%)	1(3%)	0	1(3%)
Glomerular damage		1(1%)	2(5%)	4(11%)	0	4(10%)
Scar		0	0	2(6%)	3(8%)	0
Tubule proliferation		0	2(5%)	0	5(13%)	0
Renal pelvis proliferation		3(4%)	1(3%)	3(8%)	5(13%)	10(26%)
Cast		10(13%)	6(16%)	10(28%)	4(10%)	2(5%)
Adrenals	#	75	37	31	37	35
Hemorrhage		4(5%)	4(11%)	0	0	0
Cysts		0	8(22%)	0	0	0
Fatty change		1(1%)	0	0	1(3%)	0
Uterus	#	72	34	31	32	35
ICI		0	0	1(3%)	1(3%)	1(3%)
Hypertrophy/hyperplasia		7(10%)	3(8%)	1(3%)	4(13%)	7(20%)
Polyps		6(8%)	4(12%)	1(3%)	0	3(9%)
Ovaries	#	73	37	32	36	39
Aschheim-Zondek		73(100%)	12(32%)	11(34%)	13(36%)	38(97%)
Cysts		2(3%)	3(8%)	1(3%)	1(3%)	0
Fatty change (& fat)		0	0	1(3%)	0	1(3%)
Mammary Glands	#	72	30	25	19	35
Cysts		9(13%)	3(10%)	3(12%)	1(5%)	9(26%)

† = Total examined, tissue samples
†† = inflammatory cellular infiltration
††† = previously diagnosed as bile duct adenoma

Data extracted from Bayer Report No. 4888 Histopathology Addendum and Addendum 2.

Table II presents the "updated" (including additional animals) non-neoplastic findings from the 2 year chronic rat feeding study. As can be seen from this summary table (prepared by this reviewer), no biologically significant differences in non-neoplastic findings were noted in the males, except for a statistically significant increase, $p < 0.01$, in the 100 ppm group for parasitic cell granuloma of the liver; however, this is considered to be an inflammatory response rather than a compound related effect. On the other hand, the high dose females presented with increases in bile duct proliferation, renal pelvis proliferation, hpertrophy/hyper plasia of the uterus and cysts in the mammary glands; only the renal pelvis proliferation showed a dose response relationship (statistically significant at the $p < 0.01$ level for the high dose group).

3. Clarification of nomenclature

The registrant's consultant pathologist clarified certain questions on nomenclature and definitions of histopathological findings with Dr. Louis Kasza of the Toxicology Branch. These items included reclassification of liver bile duct proliferative changes and definitions for liver "changes in the nucleus" and for "tumor" as used in the report. According to the investigators regarding bile duct lesions: "These findings were first described by Dr. Emminger many years ago. Nowadays, it is accepted that what was once termed 'bile duct adenoma' is better described as 'bile duct proliferation'". According to the investigators regarding the incidence of ovarian adenomas: "...a number of slides from the Sencor experiment was misinterpreted. Lesions such as those described as ovarian cytadenomas, represented follicular cysts. True neoplasms were found only in 2 instances - the recheck revealed granulosa cell tumours. In this respect, ovarian cystadenomas have also been overdiagnosed, and require changes. The new tumour tables have been changed accordingly".

I concur with the explanations and revisions by the registrant regarding pathological findings for this study and with the conclusions reached in this review.

Louis Kasza

Louis Kasza,D.V.M.,Ph.D.
Toxicology Branch Pathologist

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4. Body and Organ Weight Data.

In response to the request for tables of mean weekly body weight data by sex, the registrant supplied only growth curves and individual animal body weight data; no summary tables were provided. However, legible copies of the individual animal body weight data were provided and mean weekly body weights (calculated by this reviewer) at selected intervals is shown in Tables III and IV.

Table III: Mean Animal Body Weights (gms) at Selected Time Points (values calculated by the reviewer)

Dose(ppm)	Week: 0	26	53	79	105
A: Males					
Control	51.4	390.8	426.7	445.5	401.1
25	51.5	393.1	421.5	443.9	430.1
35	51.5	387.0	409.1	443.7	407.1
100	51.5	394.0	411.0	451.6	420.9
300	51.5	381.3	414.0	439.8	403.4
B: Females					
Control	52.1	238.8	255.9	270.7	258.9
25	52.1	231.4	254.5	272.6	261.1
35	52.1	242.1	259.6	283.4	270.1
100	52.1	229.4	252.0	270.2	254.1
300	52.1	221.6	243.7	262.2	256.9

Data extracted from Bayer Report No. 4888 Addendum.

Table IV: Animal Body Weight Gain At Selected Intervals (gm)

Weeks: Dose(ppm)	0-26 Males	0-53	0-79	0-105	0-26 Females	0-53	0-79	0-105
Control	339.4	375.3	394.1	349.7	186.7	203.8	218.6	206.8
25	341.4	370.0	392.4	378.6	179.3	202.4	220.9	209.0
35	335.5	357.6	392.2	355.6	190.0	207.5	231.3	218.0
100	342.5	360.0	400.1	369.4	177.3	199.9	218.1	202.0
300	329.8	362.5	388.3	351.9	169.5	191.6	210.1	204.8

Data extracted from Bayer Report No. 4888 Addendum.

These data substantiate the statement in the registration standard re-review that no significant differences were found between the control and the 25 to 100 ppm test groups through the 24 month test period. The males of the 300 ppm test group showed significant differences at weeks 70 to 80 and 90 to 100 while the females showed significant differences (for both sexes according to the investigators: $p < 0.05$) from weeks 20 to 100, but at the end of the test period there was only a slight difference from control for the females.

The absolute organ weights are presented on Table V and relative organ weights are presented on Table VI below:

Table V: Absolute Organ Weight (mg)

Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney
Male Rats						
Control	24.7	1013	1902	10191	847	2602
25	26.2	1058*	1809	11547**	921*	2510
35	26.9*	1009	1863	10880*	804	2497
100	28.6**	1029	1913	10521	915	2491
300	27.4	979	1867	9711	781	2362**
Female Rats						
Control	21.9	772	1319	8610	669	1761
25	21.5	754	1332	8411	649	1676
35	24.5	766	1483	8156	725	1767
100	20.2	715**	1231	7605**	663	1656**
300	20.9	721**	1199**	7762	613*	1705

* = $p < 0.05$
** = $p < 0.01$
Data extracted from BAYER AG Report No. 4888 Table 16a.

The absolute weights of female rat heart (significamt at 100 and 300 ppm) and lung (significant at 300 ppm) showed a dose related decrease. The absolute kidney weight in males showed a dose-related decrease with the 300 ppm level being statistically significant.

Table VI: Relative Organ Weights (mg/100 gm body weight)

Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney
Male Rats						
Control	6.2	255	408	2553	211	654
25	6.0	246	424**	2683*	215	584**
35	6.8*	250	466	2702	198	620
100	6.8*	247	458	2511	217	595**
300	6.8	243	466	2416	193	588**
Female Rats						
Control	8.7	301	519	3336	260	685
25	8.2	290	514	3236	250	646
35	9.1	285	548	3031**	270	660
100	7.9	283*	483	2999**	264	656
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* = $p < 0.05$
** = $p < 0.01$
Data extracted from BAYER AG Report No. 4888 Table 16a.

The average relative organ weights show a similar pattern except that liver weight is reduced over control in the 35, 100 and 300 ppm dosage levels.

Although these above changes were noted, they were of uncertain biological significance since there were no corroberative histological or clinical chemistry findings.

Conclusions:

Metribuzin is not oncogenic to the rat in dietary levels up to 300 ppm. The No Observed Effect Level (NOEL) for systemic effects is 100 ppm. The Lowest Observed Effect Level (LOEL) for systemic effects is 300 ppm, based on the decreased weight gain, along with the pathological changes in the liver, kidneys, uterus and mammary glands.

The sponsor has now satisfactorily responded to all requests made in the re-review of the chronic rat study and the study is upgraded to Core-Minimum Data. Assessment of the chronic toxicity/ oncogencity potential for metribuzin in the rat has included the additional data and clarifying information provided by the registrant.

APPENDIX: DER from Registration Standard for Metribuzin (1/23/85)

004767

Data Review:

Study Identification:

Study Title: BAY 94 337 Chronic Toxicity Studies on Rats (2-year feeding experiment)

EPA Identification Numbers: EPA Accession No. 112891

Sponsor: Mobay Chemical Corporation
Chemagro Agricultural Division
Kansas City, Missouri 64120

Testing Laboratory: BAYER AG
Institut fur Toxikologie
Wuppertal-Elberfeld

Report Numbers: 4888 & 41816

Date of Study: September 25, 1974

Study Director: Dr. rer. nat. Eckhard Loser

Histopathological Examination: Prof. Dr. med. U. Mohr

Test Compound: BAY 94 337 (Metribuzin) Technical (also called SENCOR)
Purity: 99.5%
Batch No.: 1603/71

Dosage: 25, 35, 100 and 300 ppm mixed with pulverized Altromin R feed (from Altrogge, Lage/Lippe).

Test Animal: SPF Rats (Wistar Strain) bred by Winkelmann, Kirchborchen, Kreis Paderborn. At start of experiment rats were about 28 to 32 days old with males having a mean body weight of 51.4 gm. and females with a 52.1 gm mean body weight.

Materials and Methods: A copy of the materials and methods section from the investigators report is appended.

Hematology examinations were performed on 5 rats per sex at 3, 6 and 12 month intervals (although Core recommends 4 month intervals). At 24 months the test were conducted on 10 rats per sex.

The hematology examination protocol was adequate and included reticulocyte counts.

The blood chemistry determination did not include Ca, PO_4, fasting glucose, urea nitrogen but did include blood sugar (not fasting) and cholesterol determinations.

Urinalysis tests were conducted on urine collected for 16 hours at 3, 6, and 12 months on 5 rats per sex and at 24 months on 10 rats per sex.

Thyroid function tests utilized 20 rats per sex for temperature studies at 6, 12 and 24 months and 5 rats per sex at 6 and 12 months and 10 rats per sex at 24 months for protein bound iodine determinations.

The investigators examined all tissues that are required by CORE, however histopathology was performed on all animals only in control and the high dose group. In the other three dose groups only selected tissues in selected animals (10 per group) were examined (see page 7, this review).

Results:

I. Clinical Observations:

The investigators observed no differences in "physical appearance and behavior from the control rats" in any of the test groups. No data was provided for these observations.

II. Clinical Data:

A. Food Consumption:

Although not stated in the table provided, the data presented for "average food consumption" is for 24 months. The "average quantity of active ingredient ingested" is stated as being "related to the animal body weight after 12 months of feeding". There was no statistical difference between groups in the amount of total food consumed, however as would be expected the males consumed more total food than the females (mean food consumption by males was 19.03 $\pm$ 0.59 g/animal/day and mean food consumption by females was 15.12 $\pm$ 0.50 g/animal/day, based on all groups combined).

When "average quantity of active ingredient ingested" is calculated, it was found that the female received more active ingredient than the male. See Table I below:

Table I: Active Ingredient (mg/kg body weight/day)

Dose (ppm)	Male	Female
Control	0	0
25	1.30	1.68
35	1.87	2.28
100	5.27	6.53
300	14.36	20.38

Data Extracted from BAYER AG Report No. 4888 Table 1.

B. Body Weight:

The investigators found no significant difference between control and the 25 to 100 ppm test groups through the 24 month test period. The males of the 300 ppm test group (from body weight curves) showed significant differences at weeks 70 to 80 and 90 to 100 while the females showed significant differences (according to the investigators: $p < 0.05$) from weeks 20 to 100, but at the end of the test period there was only a slight difference from control (for the females).

The registrants provided graphed mean data (curves) and individual weekly weight data for the animals. Numerous entries on the individual animal weekly weight data that were provided was illegible (including the "new" copy provided by the registrant).

C. Mortality:

At 12 months there was no significant mortality noted by the investigators. Survival to study termination was excellent, see Table II below. There was no apparent difference in mortality between any of the treatment groups and control.

Table II: Mortality Rates (in percent)

DOSE (ppm)	After 1 year	At study termination
Males		
Control	2.5	17.5
25	0	22.5
35	2.5	20.0
100	0	25.0
300	0	27.5
Females		
Control	0	10.0
25	2.5	12.5
35	0	22.5
100	0	17.5
300	2.5	12.5

Data extracted from BAYER AG Report No. 4888 Table 2.

D. Hematology:

At 3 months there were no significant differences in hematological parameters.

At 6 months there appears to be a slight dose related decrease in reticulocyte count in both males and females and a slight decrease in leucocytes in the male rats.

However, at the 12 and 24 month intervals there were no apparent differences in reticulocyte or leucocyte counts or other hematological parameters.

E. Liver Function Tests:

There were no significant differences between test groups at 3, 6, 12 or 24 months for male and female plasma enzyme alkaline phosphotase or the transaminases (GOT and GPT) or total protein levels.

F. Urinalysis and Kidney Function Tests:

At 3 months there was a slight increase in protein in the urine in both male and female animals of the test groups as compared to control. This was not apparent at the 6 month interval in the males, but slight increases were still seen in the females (dose related). At the 12 month interval there were no apparent differences noted and at 24 months the controls had higher levels of protein in the urine than the test groups.

G. Blood Sugar and Cholestrol Determinations:

There were no significant differences between control and test groups at the 3, 6, 12 and 24 month intervals.

1. Body temperature: There were no meaningful differences seen between control and test groups at 6, 12 and 24 months.

2. Protein-bound iodine: There were no significant differences seen between control and test groups at 6, 12 and 24 months.

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III. Necropsy Data:

The investigators stated that examination of all rats that died during the study and were autopsied showed "No pathological changes atttributable to administration of the test compound". However, for many of the animals which died during the course of the study, the comment in the table under the causes of death was stated as "not determinable due to decay of animal", see Table III below. Many of the animals showed evidence of "massive pneumonia" as the cause of death.

The investigators further state, that the animals grossly examined at final sacrifice "showed no signs of any specific damage".

Table III: Number of Animals Lost to "Decay"

DOSE (ppm)	Males	Females
Control	5/14 (36%)	4/8 (50%)
25	1/9 (11%)	2/5 (40%)
35	2/8 (25%)	4/9 (44%)
100	2/10 (20%)	0/7 (0%)
300	2/11 (18%)	1/5 (20%)

Demoninators refer to animals dying prior to end of experiment.

Data extracted from BAYER AG Report No. 4888 Tables 15a and 15b.

A. Organ Weights:

The absolute weights of female rat heart (significant at 100 and 300 ppm) and lung (significant at 300 ppm) showed a dose related decrease. The absolute kidney weight in males showed a dose-related decrease with the 300 ppm level being statistically significant. See Table IV below:

Table IV: Absolute Organ Weight (in mg)

Male Rats Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney
0	24.7	1012	1902	10191	842	2602
25	26.2	1058*	1809	11547**	921*	2510
35	26.9*	1009	1863	10880*	804	2497
100	28.6**	1029	1913	10521	915	2491
300	27.4	979	1867	9711	781	2362**
Female Rats						
Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney
0	21.9	772	1319	8610	669	1761
25	21.5	754	1332	8411	649	1676
35	24.5	766	1483	8156	725	1767
100	20.2	715**	1231	7605**	663	1656**
300	20.9	721**	1199**	7762	613*	1705

*p < 0.05
**p < 0.01

Data extracted from BAYER AG Report No. 4888 Table 16a.

The average relative organ weights show a similar pattern except that liver weight is reduced over control in the 35, 100 and 300 ppm dosage levels. See Table V below:

Table V: Relative Organ Weights (in mg/100 gm body weight)

Male Rats Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney
0	6.2	253	408	2553	211	654
25	6.0	246	424**	2683*	215	584**
35	6.8*	250	466	2702	198	620
100	6.8*	247	458	2511	217	595**
300	6.8*	243	466	2416	193	588**

Female Rats Dose(ppm)	Thyroid	Heart	Lung	Liver	Spleen	Kidney
0	8.7	301	519	3336	260	685
25	8.2	290	514	3236	250	646
35	9.1	285	548	3031**	270	660
100	7.9	283*	483	2999**	264	656
300	8.3	283*	471*	3028**	238*	668

*p < 0.05
**p < 0.01

Data extracted from BAYER AG Report No. 4888 Table 16a.

B. Histopathology:

The investigators evaluated the following organs from 66 males and 72 females in the control group and 29 males and 35 females in the high dose group: brain; pituitary gland; eyes; cervical lymph nodes; aorta; trachea; sternum including bone marrow; mammary gland; esophagus; stomach; 4 intestinal segments; pancreas; epidydimus; prostate; seminal vesicle; urinary bladder; uterus; thyroid; heart; lung; liver; spleen; kidneys; adrenal glands; testicles or ovaries; skeletal muscle with femur and sciatic nerve; salivary glands.

For the other treatment groups, the following organs of 10 animals per sex were examined: thyroid; heart; liver; spleen, kidney; adrenal gland; testicles or ovaries.

The "main" organs of animals which died during the study were also examined.

The pathologist stated that the "histological findings of the present compound investigation in Wistar rats cannot be proven to be treatment or dose dependent and it must be assumed that the found tumors lie within the range of the normal spontaneous tumor rate for this species".

The investigators supplied a summary table of "histological findings of suspected tumor material" without any reference (in the majority of the observations presented) to the organ in which the tumor was found. This reviewer utilized the provided individual histopathological findings and produced a summary table with organ by organ incidence of "suspected tumor" findings (see Table VI). As can be seen on Table VI, the females of the 300 ppm test group showed a statistically significant increase ($p < 0.01$ done by independent chi square method) over the control group for liver bile duct adenoma. A statistically significant increase ($p < 0.05$ done by independent chi square method) was also observed for pituitary ademona and a slight, but not statistically significant, increase in ovarian adenoma (23% as compared to 13% in control) was observed. Further data is required on the animals from the other 3 dosage groups along with historical control data on the incidence of these tumors in this breed of rat before evaluation of this study can be completed.

No tumors were found by the investigators in the (both sexes) aorta, bone marrow (sternum), brain, cervical lymph glands, epididymus, esophagus, eyes, heart, kidneys, lungs, skeletal muscle with femur, nerve, prostate gland, salivary gland, seminal vesicle, spleen (male), stomach (female), trachea and urinary bladder of the animals examined at final sacrifice.

Table VI: Histopathological Findings of Suspected Tumor Material
(rat sacrificied at the end of the study)

Dose (ppm):		Control	25	35	100	300
Adrenal gland- adenoma	M	8/66	1/10	1/10	0/10	1/29
	F	0/72	0/10	0/10	0/10	0/35
"Tumor"†	M	0/66	0/10	0/10	0/10	0/29
	F	0/72	0/10	2/10	0/10	0/35
Intestine- "Tumor"†	M	1/66	-††	-††	-††	0/29
	F	0/72	-	-	-	0/35
Liver-bile duct adenoma	M	19/66	10/10	8/10	5/10	9/29
	F	13/71	4/10	5/10	1/10	19/35**
Pancreas- adenoma	M	1/65	-	-	-	0/29
	F	1/71	-	-	-	1/35
Pituitary- adenoma	M	10/62	-	-	-	6/29
	F	27/71	-	-	-	21/35*
carcinoma	M	2/62	-	-	-	1/29
	F	11/71	-	-	-	5/35
Spleen- lymphoma	M	0/66	0/10	0/10	0/10	0/29
	F	0/72	0/10	(1/5)†††	0/10	(1/4)†††
Stomach- carcinoma	M	1/66	-	-	-	0/29
	F	0/72	-	-	-	0/35
Thyroid gland- adenoma	M	0/65	2/10	1/10	0/10	1/29
	F	2/72	0/10	0/10	2/10	0/35
papilloma	M	0/65	0/10	0/10	0/10	0/29
	F	3/72	0/10	1/10	1/10	0/35
Testes- interstitial cell tumor		3/66	1/10	0/10	0/10	0/29
"Tumor"†		0/66	0/10	1/10	0/10	0/29
Mammary gland- adenoma		5/72	-	-	-	0/35
Ovaries- adenoma		9/72	1/10	1/10	1/10(1/3)	8/35(2/4)
Uterus- adenoma		1/72	-	-	-	0/35
"Tumor"†		0/72	-	-	-	1/35
polyps		5/72	-	-	-	3/35

continued

Table VI continued:

* $p < 0.05$
** $p < 0.01$

† - unspecified tumor (must be explained further by the registrant).
†† - tissue not examined.
††† - number in parenthesis, animals died prior to end of experiment.

Data extracted from addendum to BAYER AG Report No. 4888.

The investigators also did not supply a summary table of non-neoplastic histopathological findings. This review again utilized the provided individual animal histopathological findings to produce a summary table (see Table VII). As can be seen in Table VII there were numerous observations of inflammatory cellular infiltration (ICI) in the heart, kidneys and trachea as well as the presence of lymphocytes in the kidneys, liver and trachea. The liver showed the most significant observation of "changes in the nucleus" with a slight increase in the males and a statistically significant increase ($p < 0.01$ done by independent chi square method) in the females of the 300 ppm test group. This observation of "changes in the nucleus" in the liver must be further defined by the registrant as must the observation listed as "tumor" (unspecified) in the table. There also was a statistically significant increase ($p < 0.05$ done by independent chi square method) in parasitic (stated as "possible" by the registrant) cellular granuloma observed in the 300 ppm males. The 300 ppm females presented with a slight, but not statistically significant, increase in incidence of cysts and of uterine hypertrophy/hyperplasia. The lungs showed evidence of emphysema, pneumonia, bronchitis, blockages, peribronchial lymphocyte infiltration and occasional hyperplasia of the bronchial mucous membrane.

Table VII: Non-neoplastic Histopathological Findings
(rats sacrificied at the end of the study)

Dose (ppm):		Control	25	35	100	300
Heart- ICI†	M	15/66(2/9)††	5/10	4/10(1/6)	4/10(1/8)	11/29
	F	22/73	1/10	1/10	4/10(1/7)	4/35(1/4)
Kidneys- ICI	M	3/66(3/6)	0/10	0/10	1/10(1/8)	0/29
	F	1/72	2/10	(1/5)	1/10	2/35
Lymphocytes	M	39/66	3/10(2/8)	4/10(2/6)	6/10	9/29
	F	15/72	2/10	3/10	0/10	2/35
Glomerular Damage	M	0/66	0/10	0/10	0/10	0/29
	F	1/72	2/10	3/10	0/10	4/35
Liver-"Changes in the nucleus"	M	6/66	3/10	3/10	3/10	4/29
	F	10/71	0/10	1/10	6/10	18/35**
Lymphocytes	M	18/66	2/10	2/10	2/10	9/29
	F	11/71	3/10	3/10(1/5)	1/10	4/35
Parasitic cellular granuloma (pcg)	M	7/66	0/10	0/10	5/10	8/29*
	F	0/72	1/10	0/10	0/10	0/35
Spleen- Mega-karyocytes	M	0/66	0/10	0/10	0/10	1/29
	F	1/72	0/10	0/10	0/10	2/35
Trachea- ICI	M	2/66	-†††	-	-	2/29
	F	2/71	-	-	-	1/35
Lymphocytes	M	4/66	-	-	-	0/29
	F	1/71	-	-	-	2/35
Mammary glands- Cysts		9/72	-	-	-	9/35
Uterus- Hypertrophy/ Hyperplasia		7/72	-	-	-	7/35

Lungs - see text for description of findings

* $p < 0.05$
** $p < 0.01$

† - ICI = Inflammatory cellular infiltration.
†† - number in parenthesis, animals died prior to end of experiment.
††† - tissue not examined.

Data extracted from addendum to BAYER AG Study No. 4888.

Conclusions:

There was no evidence of a compound related effect on hematological, clinical-chemical, urinalysis, kidney function, liver function and thyroid function test parameters. There also was no compound related effect on mortality or food consumption. However there was a statistically significant reduction of weight gain seen in the high dose (a table of weekly body weight gain data must be supplied by the registrant). Relative organ weights showed a significant decrease in heart (100 and 300 ppm females), lungs (300 ppm females), liver (35 to 300 ppm females), spleen (300 ppm females) and kidney (25, 100 and 300 ppm males), however there is a lack of dose response in these findings and there are no histopathological observations that correspond with these findings. The neoplastic histopathological observations consisted of a statistically significant increase in the incidence of adenoma of the liver bile duct and the pituitary gland in the 300 ppm females. However, not enough animals were examined histopathologically in the other 3 dosage groups to allow a judgement to be made with respect to a dose response effect of the chemical. Further data must be supplied in the form of histopathological examinations of the animals not previously examined in the other 3 dosage groups along with historical control data on the incidence of these tumors in this particular rat strain. The registrant must also explain the observation of "tumor" in certain tissues. Non-neoplastic observations showed a statistically significant increase in liver "changes in the nucleus" in the females of the 300 ppm test group. The registrant will also have to provide the non-neoplastic observations in the animals of the other 3 dosage groups that were not previously examined. No systemic No Observed Effect Level (NOEL) can be determined without this data.

The registrant is directed to provide summary tables of the neoplastic and non-neoplastic findings as produced in this review (see Tables VI and VII).

Certain biochemical parameters were not determined (Ca, PO_4, fasting glucose and urea nitrogen) and data for clinical observations was lacking.

Core Classification: Core-Supplementary Data since the oncogenic potential of the test compound cannot be fully ascertained without the above mentioned neoplastic histopathologic observations on animals of the 25, 35 and 100 ppm dosage groups. The non-neoplastic histopathologic observations are also lacking for the same group of animals. Historical control data of the incidence of neoplastic and non-neoplastic histopathological findings of the rat strain used in this study must be supplied by the registrant. The registrant must also explain the terms "changes in nucleus" and the observation of "tumor" (unspecified) seen in certain tissues on the individual animal pathology findings sheets. A table of mean weekly body weight data divided by sex for each study group must also be supplied. This study may be upgraded if the requested data is submitted and eliminates the deficiencies.

METRIBUZIN

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